TITLE OF THE INVENTION

VIRAL INTERLEUKIN-6

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a national stage filing from Priority Application PCT/EP96/ 03199, filed July 19, 1996.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

BACKGROUND AND SUMMARY OF THE INVENTION

1. Field of the Invention

The invention relates to diagnosis and treatment of diseases such as kaposi sarcoma, Castleman's disease, multiple myeloma, kidney cell carcinoma, mesangial proliferative glomerulonephritis or B cell lymphoma and relates more particularly to viral interleukin 6 for the diagnosis and treatment of human disease.

Kaposi's sarcoma (KS), a multifocal proliferative lesion of uncertain pathogenesis, is highly prevalent among homosexual AIDS patients. Studies with biopsy materials and cultured cells have indicated an important role of growth factors and cellular cytokines, such as basic fibroblast growth factor, interleukin-1β, platelet derived growth factor, interleukin-6 (IL-6), and oncostatin M for the proliferation of spindle cells in KS [1,2]. Several groups found indication for the expression of interleukin-6 (IL-6) receptors in AIDS-KS cells [3] and derived spindle cell lines [4]. As epidemiological evidence had suggested that an infectious agent other than HIV may also be involved in KS pathogenesis, it stirred considerable interest when Chang and colleagues [5] found DNA sequences of a novel herpesvirus in AIDS-KS tissues. Meanwhile, DNA of this virus was consistently found in all epidemiological forms of KS. The new virus, termed human herpesvirus 8 (HHV-8), shows marked sequence homology to *herpesvirus (h.) saimiri*, the prototype of γ_2-herpesviruses; thus HHV-8 appears to be the first human

member of γ_2-herpesviruses (genus rhadinovirus). Cloning HHV-8 DNA from KS tissues and sequencing indicates a genome organization that is generally collinear to *h. saimiri* [6].

DETAILED DESCRIPTION OF THE INVENTION

In the course of these studies we surprisingly found, adjacent to a dihydrofolate reductase gene, an open reading frame (ORF) with the coding capacity for a 204 amino acid polypeptide with marked homology to mammalian IL-6 (P-value for homology searches with NCBI-BLAST: $P \leq 10\text{-}18$; percent identity/similarity to human IL-6: 24.74%/ 46.91%; to murine: 24.23%/ 47.94%; to porcine: 25.97%/ 52.91%; to bovine: 24.60%/ 49.73%; all alignments were calculated with the GCG software "GAP").

The viral gene product (v-IL-6) has conserved all 4 cysteine residues that are known to be involved in IL-6 disulfide bridging, and it shows a characteristic signal peptide of 19 to 22 amino acids (fig. 1). The area involved in binding of human IL-6 to its receptor has been mapped to the middle of the protein by two groups[7, 8, 9]. Ehlers et al. showed that amino acids 105 to 123 of the human IL-6, as shown in fig. 1 (GFNEEtCLVKIitGLLEFE), are involved in receptor binding. Most remarkably, this region is highly conserved in v-IL-6 (GFNEtsCLkKLadGFFEFE). Identity and similarity of v-IL-6 to the receptor binding region of human IL-6 are 58% and 74%, respectively (fig. 1). This is almost identical with the degree of conservation that can be observed in this receptor binding area of human IL-6 to murine IL-6. As both human IL-6 and murine IL-6 are able to bind to the receptor of the other species (murine IL-6 and human IL-6, respectively), it is likely that v-IL-6 is also able to bind to the human and the murine IL-6 receptor.

Rhadinoviruses frequently acquire genes from their host cell [10]. This HHV-8 ORF however, is the first known example of a viral IL-6 structural homologue. Up to now all cell-homologous genes of rhadinoviruses that have been tested were functional; non-functional genes would most likely have been lost in viral evolution. Thus, the conservation of essential IL-6 features makes it highly suggestive that v-IL-6 is

1. [Viral] Isolated viral interleukin-6 (v-IL-6)[, which can be] obtained by recombinant expression of the DNA of human herpes virus type 8 ("HHV-8").

2. [A] An isolated polypeptide[, which can be] obtained by recombinant expression of the DNA of HHV-8, and which comprises the amino acid sequence (SED ID NO:2) of [fig]. FIG. 2.

3. [A] An isolated polypeptide having the amino acid sequence (SEQ ID NO:2) of [fig.] FIG. 2.

4. A fragment of v-IL-6[, having the capability of binding to] that binds an interleukin-6 ("IL-6") receptor and [comprising] comprises the amino acid sequence (residues 87-105 of SEQ ID NO:2) GFNEtsCLkKLadGFFEFE.

5. No changes.

6. No changes.

7. Cancelled.

8. A fragment obtained from the of the v-IL-6 [as claimed in] of claim 1[, characterized in that it is able to competively] that can be competitively inhibit the biological activity of IL-6 in a suitable assay system.

9. An isolated nucleic acid molecule coding consisting essentially of the sequence of SEQ ID NO:1 and coding for v-IL-6, which is obtainable by recombinant expression of the DNA of human herpes virus type-8 (HHV-8).

10. An isolated nucleic acid molecule consisting essentially of the sequence of SEQ ID NO:2 and coding for a polypeptide, which is obtainable by recombinant expression of the DNA of HHV-8 and which comprises the amino acid sequence of [Fig.] FIG. 2.

11. An isolated nucleic acid [having] consisting essentially of the nucleotide sequence of [fig.] FIG. 2.

12. No changes.

13. No changes.

14. No changes.

15. No changes.

16. Testkit for the detection of v-IL-6 DNA or RNA, comprising a nucleic acid molecule consisting essentially of the sequence of SEQ ID NO:1 as claimed in claim 11.

17. A pharmaceutical composition which may be used in treatment comprising as an active ingredient an IL-6-inhibiting an effective amount of an antibody as claimed in claim 13 and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition which may be used in treatment comprising as an active ingredient the polypeptide as claimed in claim 2 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition which may be used in treatment comprising as an active ingredient the nucleic acid as claimed in claim 11 and a pharmaceutically acceptable carrier.

20. Cancelled.

21. Cancelled.

22. Cancelled.

23. Cancelled.

24. Cancelled.

25. Cancelled.

26. Cancelled.

27. Cancelled.

28. No changes.

29. No changes.

30. No changes.

31. No changes.

32. No changes.

33. No changes.

35. The method of claim 34, wherein said cells which may be used in treatment are selected from the group consisting of β-lymphocytes, hybridomas, hemopoietic and endothelial cells.